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# Acute lower limb ischemia due to thrombo-embolic arterial occlusions in two previously healthy men with markedly elevated Lp(a)

Gabriella V Bedarida, Ulrich Hoffmann and Federico Tatò

**Abstract:** Lipoprotein (a) (Lp(a)) is a well-documented risk factor for atherosclerotic cardiovascular disease. Its role in acute thrombo-embolic occlusions of peripheral arteries is not known. We describe two cases of multiple, acute, peripheral arterial occlusions in two previously healthy men with markedly elevated Lp(a). Both cases had unsatisfactory results after percutaneous and surgical revascularization procedures. Experience yielded in these two cases suggests that when an unfavorable outcome occurs in a peripheral artery disease patient in the absence of the regular risk factors, Lp(a) should be determined and its role investigated.

**Key words:** acute limb ischemia; arterial thrombosis; Lp(a); myointimal hyperplasia; peripheral artery disease

## Introduction

Elevated lipoprotein (a) (Lp(a)) is an established risk factor for atherosclerosis and has been linked to premature coronary artery disease as well as stroke and peripheral artery disease (PAD).<sup>1–3</sup> Lp(a) possesses unique antifibrinolytic and prothrombotic properties, and may play an important role in vascular thrombosis.<sup>1,4</sup> However, elevated Lp(a) has not previously been recognized as a risk factor for acute thrombo-embolic occlusions of peripheral arteries. We report the cases of two adult men with markedly elevated Lp(a) and multifocal thrombo-embolic occlusions of the iliaco-femoral and popliteo-crural arteries in the absence of advanced atherosclerosis.

## Case reports

### Case 1

A 54-year-old previously healthy white male presented to our clinic with a 3-week history of right-sided calf

and foot claudication. His past medical history was significant only for a recently developed impotence, for which he had received three monthly testosterone injections. He had no history of smoking, diabetes, hypertension, hypercholesterolemia, and no family history of premature cardiovascular disease.

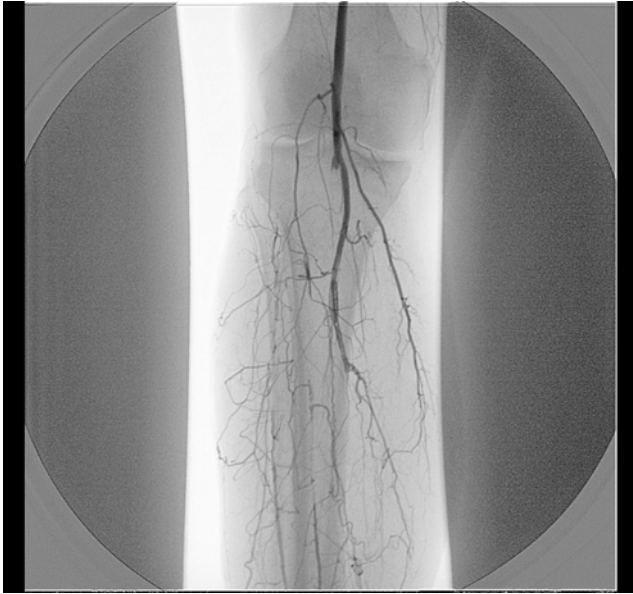
The physical examination and non-invasive vascular laboratory tests showed bilateral, distal PAD with impaired hemodynamic function at the level of the right calf and left foot. Duplex ultrasound showed hypoechogenic occlusion of the right popliteal artery in the absence of arteriosclerosis or aneurysm. The patient underwent an extensive work-up including a 24-hour Holter monitor, transesophageal echocardiogram and aortic imaging to rule out embolic disease. Laboratory tests including markers of inflammation (ESR, CRP), electrophoresis, antinuclear and anticardiolipin antibodies and tests for thrombophilia (fibrinogen, ATIII, protein C and S, activated protein C) were normal. Homocysteine was 13.2  $\mu\text{mol/l}$  (normal values  $<13.9 \mu\text{mol/l}$ ). Lipid and lipoprotein analysis showed normolipidemia (total cholesterol 203 mg/dl, LDL-cholesterol 120 mg/dl, HDL-cholesterol 55 mg/dl, triglycerides 153 mg/dl). Lp(a) was measured with a commercial turbidometric immunoassay (Wako, Japan) with a normal reference range of  $<30 \text{ mg/dl}$  and it was markedly elevated at 86 mg/dl.

Digital subtraction angiography (DSA) showed occlusion of the popliteal artery of the right leg (Figure 1), and occlusion of the posterior and anterior tibial arteries of the left leg with thrombo-embolic

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**Figure 1** Digital subtraction angiography of the right leg in patient 1: occlusion of the popliteal artery at the level of the knee joint space and of the proximal crural vessels with thrombo-embolic appearance.

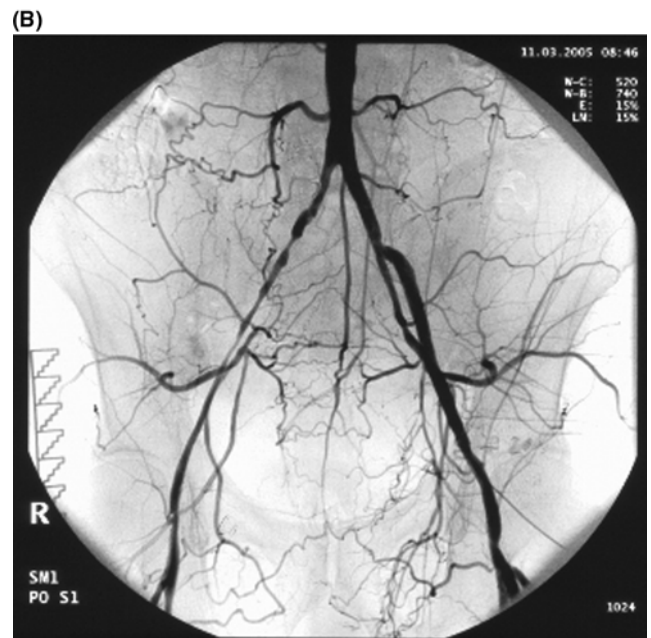
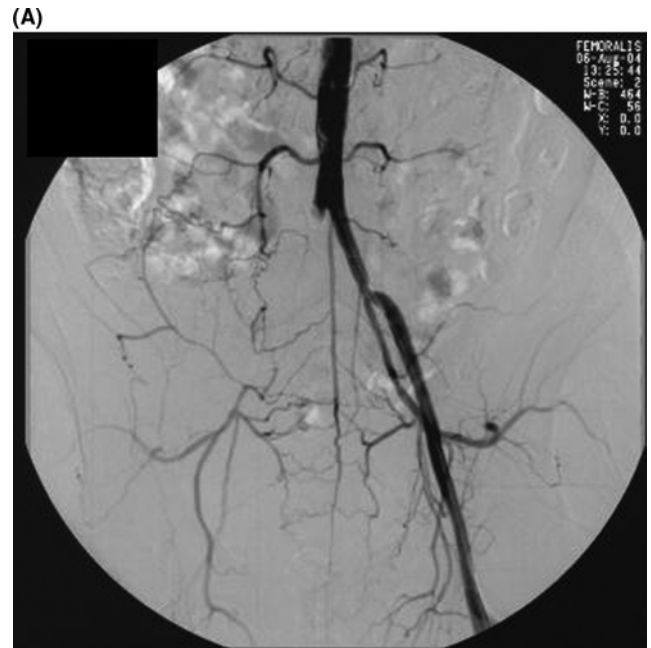
appearance. Percutaneous recanalization of the right popliteal artery was attempted by catheter-directed thrombolysis with urokinase followed by aspiration thrombectomy and percutaneous transluminal angioplasty (PTA). All procedures were unsuccessful. The patient was treated with oral anticoagulation and walking exercise. After 3 months the patient showed marked symptomatic and hemodynamic improvement.

## Case 2

A 54-year-old, previously healthy white male presented at another hospital with acute, critical ischemia of the right leg. Angiography revealed occlusions of the right common and external iliac artery (Figure 2A) and of the left tibio-peroneal trunk. Surgical thrombectomy of the right iliac artery required two interventions because of early re-occlusion, and was unsuccessful in the left tibio-peroneal trunk. He underwent an extensive work-up including a 24-hour Holter monitor, transesophageal echocardiogram and aortic imaging to rule out embolic disease. At the time of discharge from the hospital ankle-brachial indices were normal and walking distance unlimited.

The patient was first seen at our clinic 8 months later complaining of a 5-month history of bilateral calf claudication. He had no history of diabetes, hypertension, hypercholesterolemia, and no family history of cardiovascular disease. He had quit smoking 1 year previously after a 12-pack year history.

Physical examination and non-invasive vascular laboratory tests showed bilateral PAD with impaired hemodynamic function at the level of the right thigh and left calf. Laboratory tests including markers of



**Figure 2** Digital subtraction angiography of the aortoiliac vessels in patient 2 at the time of initial presentation (A), and 8 months after surgical revascularization (B). The first angiogram shows acute, thrombo-embolic occlusion of the right iliac arteries, and the second angiogram shows high-grade, myointimal restenosis.

inflammation (ESR, CRP), electrophoresis, anti-nuclear and anticardiolipin antibodies and tests for thrombophilia (fibrinogen, ATIII, protein C and S, activated protein C) were normal. Homocysteine was  $9.2 \mu\text{mol/l}$  (normal values  $<13.9 \mu\text{mol/l}$ ). Lipid and lipoprotein analysis showed a borderline hypercholesterolemia (total cholesterol  $209 \text{ mg/dl}$ , LDL-C  $147 \text{ mg/dl}$ , HDL-C  $40 \text{ mg/dl}$ , triglycerides  $108 \text{ mg/dl}$ ). Lp(a), measured with a commercial turbidometric

immunoassay (Wako), was markedly elevated at 81 mg/dl (normal >30 mg/dl).

DSA performed at an outside facility a few days prior to presentation showed diffuse, high-grade restenosis of the right common and external iliac artery (Figure 2B), and of the left popliteal artery. Duplex ultrasound showed circular, hypoechogenic wall thickening in the affected arteries consistent with myointimal hyperplasia. We recommended PTA of the right iliac artery. The patient wished to undergo the intervention at an outside facility and was lost to follow-up. From a telephone contact, he is experiencing persistent bilateral claudication despite repeated interventions.

## Discussion

We present the cases of two men with severe PAD due to multiple, thrombo-embolic arterial occlusions in the absence of advanced arteriosclerosis and traditional cardiovascular risk factors. Markedly elevated Lp(a) above 80 mg/dl was identified as the only significant laboratory abnormality. The morphology of the occlusions and the acute onset of symptoms suggest either embolism or local arterial thrombosis. A source of embolism could not be identified. However, embolism of unknown origin remains a possibility. Other etiologies of non-arteriosclerotic PAD such as thrombangiitis obliterans, large-vessel vasculitis, or popliteal entrapment have either been ruled out or appear very unlikely based on the clinical presentation and vascular morphology.

Elevated Lp(a) is a well-established risk factor for cardiovascular disease<sup>2</sup> and it has also been shown to be a strong predictor of peripheral vascular disease, independently of cigarette smoking and diabetes in a group of 100 white male patients with mean age of 67 years.<sup>5</sup> In a case-control study of 50 white men under the age of 45 years with PAD, an elevated Lp(a) (>30 mg/dl) was an independent risk factor for the development of premature peripheral vascular disease. No association was found for homocysteine, antiphospholipid antibodies, antithrombin III, and protein C and S.<sup>6</sup> In a similar retrospective study in 55 white men, an elevated Lp(a) was specifically and independently associated with premature PAD but not with premature coronary artery disease.<sup>3</sup> However, patients in these studies presumably had arteriosclerotic PAD. To our knowledge this is the first report of highly elevated Lp(a) in patients with an initial diagnosis of PAD due to acute arterial thrombo-embolic occlusions.

The structural homology of apolipoprotein (a) with plasminogen confers Lp(a) unique antifibrinolytic and prothrombotic properties.<sup>1,4</sup> Several lines of evidence suggest that Lp(a) may be a risk factor for thrombotic vascular disorders unrelated to arteriosclerosis. Elevated Lp(a) has been linked to venous

thrombo-embolism,<sup>7</sup> childhood ischemic stroke,<sup>8</sup> left atrial thrombus,<sup>9</sup> and pregnancy loss.<sup>10</sup>

Another remarkable feature of the two presented cases is the unsatisfactory outcome after percutaneous and surgical vascular interventions. Elevated Lp(a) has been previously recognized as a risk factor for short-term, myointimal restenosis after interventions in peripheral arteries.<sup>11</sup> In a prospective study of 139 consecutive patients with successful PTA of the femoropopliteal area, the group who developed re-stenosis or re-occlusion within 1 year had a higher Lp(a) than the group without re-stenosis (59 vs 28 mg/dl). This was independent of all other risk factors, which were equally distributed between the two groups.<sup>12</sup> Moreover, Lp(a) has been shown to accumulate specifically at sites of initial myointimal hyperplasia in an animal model after arterial injury caused by balloon angioplasty.<sup>13</sup>

Patient 1 received testosterone replacement therapy prior to the occurrence of claudication. We cannot exclude that the hormonal therapy was a precipitating event for the thrombotic disease. The net effect of testosterone on the cardiovascular risk profile is unknown and both beneficial and deleterious effects have been recorded.<sup>14</sup> We found one report of acute limb-threatening ischemia due to thrombosis of femoropopliteal and crural arteries after treatment with the synthetic androgen danazol, which was, however, mediated by severe thrombocytosis.<sup>15</sup>

Although our findings need to be confirmed in other cases, we believe that markedly elevated Lp(a) may have played an important causative role in the presented two cases of acute PAD due to thrombo-embolic arterial occlusions. We suggest that it may be worthwhile to measure Lp(a) in young patients with PAD with unexplained, acute, arterial occlusions and lack of other traditional risk factors.

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